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**UTILITY
PATENT APPLICATION
TRANSMITTAL**

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No. GSI-005

First Inventor or Application Identifier Osgood

Title Method and Apparatus for Washing...

Express Mail Label No. EL110241595US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification [Total Pages 35]
(preferred arrangement set forth below)
 - Descriptive title of the invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the invention
 - Brief Summary of the invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 6]
4. Oath or Declaration [Total Pages 4]
 - a. ☒ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

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5. ☐ Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. ☒ Assignment Papers (cover sheet & document(s))
8. ☐ 37 C.F.R. § 3.73(b) Statement of Power of Attorney (when there is an assignee)
9. ☐ English Translation Document (if applicable)
10. ☐ Information Disclosure Statement (IDS)/PTO-1449 [Copies of IDS Citations]
11. ☐ Preliminary Amendment
12. ☐ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
13. ☐ * Small Entity Statement filed in prior application, Status still proper and desired (PTO/SB/09-12)
14. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. ☐ Other: _____

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. _____ / _____

Prior application information: Examiner _____ Group / Art Unit: _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

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or ☒ Correspondence address below

Name	Rajesh Vallabh				
Address	Hale and Dorr LLP 60 State Street				
City	Boston	State	MA	Zip Code	02109
Country	USA	Telephone	(617) 526-6000	Fax	(617) 526-5000

Name (Print/Type)	Rajesh Vallabh	Registration No. (Attorney/Agent)	35,761
Signature	<i>Rajesh Vallabh</i>	Date	June 5, 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Attorney Docket No. GSI-005)

In re Application of:)
OSGOOD et al.) Examiner: Not Yet Assigned
Serial No. Not Yet Assigned) Art Unit: Not Yet Assigned
Filed: Herewith)
For: METHOD AND APPARATUS FOR WASHING)
AND DRYING PINS IN MICROARRAY)
SPOTTING INSTRUMENTS)

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Assistant Commissioner for Patents
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Sir:

TRANSMITTAL LETTER

Enclosed herewith for appropriate action by the United States Patent and Trademark Office are the following documents:

1. New Utility Patent Application Transmittal (37 C.F.R. §1.53(b)), (*in duplicate*) including:

- 19 Pages of Specification
- 15 Pages of Claims
- 1 Page of Abstract
- 6 Sheets of Informal Drawings (Figs. 1 through 14)

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Serial No.: TBA
Page 2

2. Executed Combined Declaration and Power of Attorney;
3. Assignment together with Recordation Form Cover Sheet (*in duplicate*)
(Form PTO-1595); and,
4. Return Postcard.

Please send all correspondence related to the subject application to:

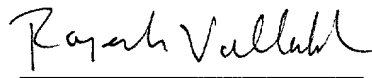
**Rajesh Vallabh
Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109**

The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment to Deposit Account No. 08-0219.

Dated: June 5, 2000

Hale and Dorr LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000

Respectfully submitted,
HALE AND DORR LLP



Rajesh Vallabh
Reg. No. 35,761
Attorney for Applicants

METHOD AND APPARATUS FOR WASHING AND DRYING PINS IN MICROARRAY SPOTTING INSTRUMENTS

Background of the Invention

5 Field of the Invention

The present invention relates generally to microarray spotting instruments and, more particularly, to a method and apparatus for washing and drying pins in such instruments.

10 Description of Related Art

As is well known (and described, e.g., in U.S. Patent No. 5,807,522 issued to Brown et al. and in "DNA Microarrays: A Practical Approach," Schena, Mark, New York, Oxford University Press, 1999, ISBN 0-19-963776-8), microarrays are arrays of very small samples of purified DNA or protein target material arranged as a grid of
15 hundreds or thousands of small spots on a solid substrate. When the microarray is exposed to selected probe material, the probe material selectively binds to the target spots only where complementary bonding sites occur, through a process called hybridization. Subsequent quantitative scanning in a fluorescent microarray scanner may be used to produce a pixel map of fluorescent intensities (See, e.g., U.S. Patent
20 No. 5,895,915 issued to DeWeerd et al.). This fluorescent intensity map can then be analyzed by special purpose quantitation algorithms, which reveal the relative concentrations of the fluorescent probes and hence the level of gene expression, protein concentration, etc., present in the cells from which the probe samples were extracted.

25 Microarray spotting instruments (also known as "spotters") are used to place the small samples of DNA, protein, or other target biological material onto the microarray substrates. The spotting instruments retrieve the target material from

wells in a reservoir plates and "print" target spots in arrays on the microarray substrates. The reservoir plates are typically 96-well or 384-well plates, although other types are also used. Microarrays often have thousands or tens of thousands of target spots, with each spot being of a target compound from a different well of a plate.

FIGURE 1 is a simplified block diagram of components of a typical spotter 10. The spotter 10 includes (1) a plate-holding well station 12, which holds one or more reservoir plates, (2) a substrate holding station 14, which holds a plurality of microarray substrates (typically 20 – 100 substrates), (3) a printhead 16, which holds a plurality of microarray spotting pins (shown, e.g., in FIGURE 2), (4) a pin washing and drying apparatus 18, and (5) an actuator system 20, which includes robotic manipulator arms for moving the printhead in X, Y and Z directions relative to the plates, substrates and the washing and drying apparatus. The spotter is enclosed in an enclosure 21 to provide a humidity controlled environment.

FIGURE 2 shows a side view of a simplified printhead 16 holding a plurality of pins 22. For convenience of illustration, only two pins 22 are shown, although a typical printhead will hold many more pins. Pins typically include a pinhead 24, a pin shaft 26 and a tapered pin tip 28. The printhead 16 comprises a block of material, typically metal, that includes an array of through-holes. The through-holes are slightly larger than the outer diameter of the pin shafts 26 so the shafts can extend through the through-holes. The through-holes are also smaller than the outer diameter of the pin heads 24 so that when the pin shaft 26 is dropped into one of the through-holes, the pin head 24 will be supported by the upper surface of the printhead 16. The pins are thereby "slip-fit" into the through-holes of the printhead.

Pins are commercially available in several distinct forms. The simplest pins are solid pins. These pins are simple and robust, but in being dipped into the target material in a well typically only take up enough material to form one spot. This

then requires the spotting instrument to dip the pin once for every microarray spot that is to be printed.

More commonly used pins are multi-spot dispensing pins that can hold enough target material from a sample reservoir to form multiple spots before they need to be re-dipped in the reservoir. One such type of multi-spot dispensing pin is a slotted pin (shown in FIGURE 3), which has a gap or slot 30 at the pin tip 28. One example of such a pin is the MicroQuill brand pin available from Majer Precision Engineering, Inc. This type of pin draws fluid into the gap or slot 30 by capillary action, and deposits a small amount onto the substrate. The amount forming a spot is small compared to the sample uptake volume, so that each dip of the pin into sample liquid takes up enough sample material to print about 50-250 nearly identical spots without re-dipping in the sample plate.

A spotting cycle of a microarray spotting instrument 10 for printing a batch of microarrays is generally as follows: (1) the printhead 16 is moved to the well station 12 and positioned such that the pins 22 are located directly above particular respective wells of a reservoir plate; (2) the printhead 16 is lowered to dip the pins in respective wells, allowing each pin to take up an aliquot of sample; (3) the printhead 16 is moved to the substrate station 14 and positioned above the first substrate to be printed; (4) the printhead 16 is lowered, allowing the tips of the pins to make contact with the substrate, thereby depositing spots of target material on the substrate; (5) the printhead 16 is lifted (so that the pins are no longer in contact with the substrate) and moved to a position above the next substrate to be printed, and the printing motion is repeated; (6) printing is repeated until all substrates in the batch have been printed with these particular samples; (7) the printhead 16 is then moved to a pin washer of the wash/dry apparatus 18, and the pins are washed by dipping them in a wash solution; (8) the printhead 16 is moved to the pin dryer also of the wash/dry apparatus 18, where the pins are dried by inserting them in a

vacuum dryer; (9) the wash/dry sequence is repeated two or three times; and (10) the printhead 16 is moved to a position such that the pins 22 are above the next target material to be taken up and the entire cycle is repeated until all desired samples have been printed on the batch of substrates.

5 As indicated above, microarrays are typically spotted in batches, where the spotter is loaded with a plurality of substrates and the spotting operation produces multiple spotted microarrays, all of which are substantially identically printed. Each microarray typically is spotted so that it has between hundreds and tens of thousands of spots, where each spot comprises the dried residue of a liquid droplet
10 transferred or printed by a pin. The printhead is typically fitted with between 4 and 64 pins, which perform all of their operations in parallel.

 After printing the last substrate with a given sample, the pins are washed and dried. This step is important because if the remaining sample is not adequately removed from each pin, the subsequent spots printed by the pin will be
15 contaminated by the "carry-over" from the previous sample. Also, samples in wells subsequently dipped will be contaminated when the pin is dipped for sample uptake. Cross-contamination of samples in a microarray or plate would be very problematic in a microarray application because the hybridization and analysis processes occurring after spotting are based on the assumption that each spot is a
20 single, pure sample and not some mixture of unknown proportions.

 Prior art spotters utilize separate pin washing and pin drying devices at the wash/dry station 18. The washing is typically accomplished by dipping the pin tips into a reservoir of wash fluid, typically distilled or filtered water. FIGURE 4 illustrates one prior art pin washer 50, in which the wash fluid is kept flowing
25 through a wash chamber 52, in which the pins are dipped. Wash fluid is introduced into a small, open input chamber 54 by a tube fed by a peristaltic pump. The tube is connected to a wash fluid input port 55. The fluid flows over a weir or dam 56 into

the slightly larger washing chamber 52. The two-chamber approach allows any sediment in the wash fluid to settle out in the input chamber 54 before the fluid is brought into contact with the pins 22. A wash fluid output or drain port 58 drains fluid from the chamber 52.

5 Dipping the pin tips in the fluid in the wash chamber 52 causes the pins 22 to take up wash fluid by capillary action in the pin tip slot 30, similar to the way the pins take up sample from the reservoir plates. This dilutes the remaining sample in the pin slot reservoirs.

As shown in FIGURE 5, in another prior art wash device 70, an ultrasonic
10 transducer 72 (sometimes called a sonicator) is provided to introduce micro-cavitation in the wash fluid in the wash chamber 74. Sonication is a more effective washing process than the dipping and diluting process of FIGURE 4. However, repeated sonication is not recommended because the split tips of pins (defining the slot 30) can act as tuning forks and resonate sympathetically with the ultrasonic
15 signal. This can lead to the pin tip oscillating at high amplitudes and damaging the critical and fragile surfaces near the pin tip.

With the prior art dipping type pin washers, there is a possibility of cross-contamination between pins. The pins of a printhead, which have multiple sample types on them, are dipped simultaneously in the wash fluid, which is a liquid
20 solvent chosen for its ability to dissolve the reagents carried by the pins. The pins are typically only 4.5 to 9.0 mm apart, and some transport of mass from one pin to another during the dip washing process is inevitable even though the likelihood of gross contamination is small.

The pins are then withdrawn from the wash fluid and the printhead is moved
25 to a separate pin drying device. A typical prior art pin dryer 80 is shown in FIGURE 6. The pin dryer 80 works by applying vacuum to a plenum chamber 82 below a dryer top plate 84. A vacuum line connects a vacuum pump to the chamber 82

through a port 86. The pin tips are inserted into holes 88 in the dryer top plate 84, and the vacuum below causes ambient air to flow past the pin tips at high velocity and low pressure. These conditions cause the pins, including the slot fluid reservoir in the pin tip, to be dried in about 2 – 10 seconds. Since the fluid that was dried in and on the pin was diluted by the first washing step, and not entirely washed away, dried residue of diluted sample remains on the pin surface after drying. For this reason, the washing step is repeated at least twice and sometimes as many as four times, with each washing causing a further dilution of the residue in and on the pin until it is inconsequential.

The performance of a vacuum pin dryer 80 depends on the velocity of the air drawn past the pins and on the humidity of that air. Many spotters provide humidity-controlled environments within their enclosures 21, with humidity typically about 55%-65%. Air with that level of humidity is considerably less effective for drying pins than air at the 30%-45% humidity levels most commonly found in office and laboratory environments. The drying time and/or the air velocity must be increased to retain dryer effectiveness at the higher humidity level. Also, vacuum dryers that obtain their air supply from the humidified enclosure 21 generally pump that humidified air out to the atmosphere, placing an additional load on external humidity generating mechanisms and humidity controlling mechanisms.

Prior art dryers typically utilize vacuum pumps of linear piston or rotary vane type, with volume flow ratings in the 1 – 5 cfm range. When these pumps are applied to dryers with 32 or more pin holes, the air velocity around the pins is generally in the 2 – 10 m/sec range. Under these conditions, drying times are rarely less than 3 seconds and can be as long as 10 seconds or more. In some instruments, users often block off any dryer holes not being used (as the printhead is often not fully populated with pins) with tape, to increase the velocity of the air in the holes of

the dryer that are being used.

The timing of a typical prior art spotting cycle for printing material from one dip into the sample plate onto a batch of 20 microarrays is as shown in the following table:

5

Operation	Time (sec.)	Number of operations per cycle	Total time (sec.)
Move to sample plate position, dip pins, and withdraw pins.	3	1	3
Move to first printing position over a substrate, print, and withdraw pins.	1.2	1	1.2
Move to next substrate, print, and withdraw pins (repeated 19 more times).	1.2	19	22.8
Move to washer, dip, and withdraw	2	3	6
Move to dryer, insert pins, hold in dryer for three seconds, and withdraw pins.	4	3	12
Total time			45

Of the 45 seconds needed for one printing cycle, 18 seconds or 40% of the time is spent on washing and drying the pins. Accordingly, a quicker washing/drying process would significantly increase the throughput of the spotting instrument.

10

Many microarrays have over 10,000 unique spots printed on them. Most printheads are fitted with no more than 8 or 16 pins since greater numbers of pins cause the footprint of the printed array to be large, which leads to experimental complications at a downstream hybridization step. Printing 10,000 spots with 16 pins requires 625 dip - print - wash/dry cycles in the spotter. Printing 10,000 spots with 8 pins requires 1,250 cycles, of which over six hours (22,500 seconds) is devoted to washing and drying. Thus, the amount of time required to perform the washing and drying can be a significant portion of the total time required to spot a batch of microarrays and also can be a long time period per batch in absolute terms.

15

A need exists for a faster and more efficient method and apparatus for washing and drying microarray spotting pins in order to improve the throughput of microarray spotting instruments.

Brief Summary of the Invention

The present invention is directed to a method and apparatus for quickly and efficiently washing and drying spotting pins used in the operation of microarray spotting instruments. The apparatus includes a housing having an array of
5 upstanding tubes, each defining a chamber for receiving one of the pins of the spotting instrument. To wash the pins, streams of wash fluid are directed at the pins through inlet ports in the tubes. To dry the pins, a gas such as air is flowed through the tubes over pin surfaces. Pins can thereby be washed and dried without having to be moved. The gas used in drying the pins is preferably air of low humidity from
10 outside an enclosure containing the spotting instrument in order to reduce drying time. The time needed for washing and drying pins is thereby reduced, increasing the throughput of the spotting instrument.

These and other features and advantages of the present invention will become readily apparent from the following detailed description wherein
15 embodiments of the invention are shown and described by way of illustration of the best mode of the invention. As will be realized, the invention is capable of other and different embodiments and its several details may be capable of modifications in various respects, all without departing from the invention. Accordingly, the drawings and description are to be regarded as illustrative in
20 nature and not in a restrictive or limiting sense with the scope of the application being indicated in the claims.

Brief Description of the Drawings

For a fuller understanding of the nature and objects of the present invention, reference should be made to the following detailed description taken in connection with the accompanying drawings wherein:

5 FIGURE 1 is a simplified block diagram of a prior art microarray spotting instrument.

FIGURE 2 is a side view of a prior art printhead of the spotting instrument holding microarray pins.

10 FIGURE 3 is an enlarged side view of the tip of a prior art pin having a slot reservoir.

FIGURE 4 is a cross-section view of a prior art flowing fluid bath pin washer.

FIGURE 5 is a cross-section view of a prior art ultrasonic pin washer.

FIGURE 6 is a cross-section view of a prior art pin dryer.

15 FIGURE 7 is a simplified block diagram of a pin washer/dryer system in accordance with the present invention.

FIGURE 8A is a top view of a washer/dryer assembly of the washer/dryer system in accordance with the present invention.

FIGURE 8B is a cross-section view of the washer/dryer assembly taken generally along line 8B-8B of FIGURE 8A.

20 FIGURE 9A is a top view of a tube of the washer/dryer assembly in accordance with the invention.

FIGURE 9B is a cross-section view of the FIGURE 9A tube.

FIGURE 10 is an enlarged cross-section view of the tube, illustrating fluid flow therethrough.

25 FIGURE 11 is a top view of an alternative tube in accordance with the invention.

FIGURE 13 is a cross-section view of yet another alternative tube in accordance with the invention.

FIGURE 14 is a simplified block diagram of a microarray spotting instrument in accordance with the invention illustrating dryer air venting.

Detailed Description of Preferred Embodiments

The present invention is directed to a method and apparatus for quickly and efficiently washing and drying microarray spotting pins, particularly pins of the type having slot reservoirs. The invention, however, is not limited to such pins and
5 can be used with a variety of pins including, e.g., solid pins, grooved pins, etc..

Briefly, the inventive apparatus comprises an integrated pin washer/vacuum dryer system that allows pins to be washed and dried while substantially in one position, i.e., without requiring significant movement of a printhead holding the pins between washing and drying cycles. Generally, in accordance with the
10 invention, instead of dipping pins in a wash solution and diluting residual sample material in the slot reservoir of the pins as with the prior art, pins are washed by directing one or more streams of wash fluid at them with some velocity in a turbulent air environment. Actively flowing wash fluid on the pin circulates the fluid through the slot reservoir, causing rapid dilution of the residual sample,
15 generally without need for intermediate drying. Streams directed horizontally at the side opening of the reservoir slot while air is flowing vertically at a similar velocity are particularly effective at removing residual sample. To dry the pins, a gas such as air is flowed across pin surfaces.

FIGURE 7 is a block diagram of a pin washer/dryer apparatus 100 in
20 accordance with the invention. The apparatus 100 includes a washer/dryer assembly 102, in which the pins are washed and dried as will be described below. Wash fluid from a wash fluid container 104 flows through the assembly 102 and is collected in a waste fluid container 106. Flow of wash fluid into the assembly 102 is pressurized by, e.g., an air compressor 108. A variety of other pressure applying
25 devices can alternatively be used including, e.g., gear, peristaltic or other types of liquid pumps applied directly to the wash fluid. A vacuum is applied to draw wash fluid and air from the assembly 102 using, e.g., a vacuum pump 110.

FIGURES 8A and 8B show top and front cross-section views, respectively, of a representative washer/dryer assembly 102. The assembly 102 includes a structure comprising an array of upstanding tubes 120 arranged in a housing 122. As will be described below, each tube 120 defines a pin chamber configured to receive a pin tip. The assembly 102 shown in the drawings is designed for washing pins in a 32 pin printhead. This is exemplary only as a washer/dryer assembly in accordance with the invention can be made in a variety of sizes to accommodate different sized printheads. The assembly 102 includes one or more wash fluid input ports 124 for receiving wash fluid from the container 104. As shown in FIGURE 8B, the assembly 102 also includes a receptacle, more particularly a vacuum plenum chamber, 126 from which waste wash fluid and air from the tubes are withdrawn through a vacuum port 128. A vacuum line from the waste fluid container 106 is connected to the port 128.

FIGURES 9A and 9B are top and cross-section views, respectively, of a representative tube 120 in the washer/dryer assembly 102. As discussed below, each tube includes openings for flow of wash fluid and gas therethrough. The wall defining the tube 120 includes one or more wash fluid inlet ports 130. The preferred embodiment includes four inlet ports 130, and four streams of wash fluid enter the tube 120 through the ports 130. When wash fluid under positive pressure is applied to the outer wall of this tube 120, the fluid enters through the ports 130 in streams (indicated by arrows 132 in FIGURE 10 impinging upon a pin tip inserted in the tube 120. The wash fluid ports 130 are preferably aligned so that two of the ports 130 produce streams that are parallel to the slot 30 in the pin. The wash fluid streams are directed to strike the pin tip at or near the root of the pin slot 130 when a pin is inserted in the tube.

The inner diameter of the tube 120 is in the range of about 1.5 – 2.5 times the diameter of the largest portion of the pin tip inserted in the tube. With a pin

diameter of 1.5 mm, tubes with inner diameters of 2.2 to 3.0 mm have been found to be effective. Also wash fluid ports 130 having 250 micron and 350 micron diameters have been found to be effective, although larger and smaller ports can also be used. The wall thickness can have a fairly wide range, e.g., 250 microns to 500 microns.

- 5 The tube 120 preferably comprises stainless steel hypodermic tubing material, e.g., of type 316W or type 304 stainless steel. Such tubing is available from, e.g., Small Parts, Inc., Miami Lakes FL 33014 (sample part numbers O-HTXX-12 and O-HTXX-9).

10 In the tube 120, the inlet ports 130 are configured such that wash fluid is directed generally radially towards the center of the tube. Other inlet port configurations are also possible. For example, FIGURE 11 is a top view of an alternative washer/dryer tube 120' in accordance with the invention. Unlike the tube 120 shown in FIGURES 9A, 9B, and 10, the tube 120' includes wash fluid ports 130' that are oriented in a slightly off-center direction, i.e., the wash fluid ports 130' are angled to direct wash fluid in a direction away from the tube center, creating a swirling wash pattern. The wash fluid ports can also be oriented in various other directions. For example, FIGURE 12 shows a tube 120'' having wash fluid ports 130'' angled downwardly. FIGURE 13 shows a tube 120''' having wash fluid ports 130''' angled upwardly. Although not shown, tubes could also be provided with wash fluid ports that are angled upwardly or downwardly in combination with an off-center orientation.

25 Different types of pins protrude from the bottoms of the printheads various distances, ranging from about 10 mm to about 20 mm. It is advantageous to retain a clearance between the bottom of the printhead and the top of the washer/dryer assembly of at least 3 mm, and preferably 6 or 7 mm. When the drying function (as described below) is activated, a large volume of air (indicated in FIGURE 10 by arrows 134) flows into the space between the bottom of the printhead and the top of

the washer/dryer assembly. A sufficient clearance allows air flow without a large pressure drop.

Washing times (the time during which fluid streams are expelled from the wash fluid ports 130) can vary, e.g., from 0.5 to about 3 seconds, depending on the type of wash fluid, the pressure of the wash fluid, and the diameter of the wash fluid ports. With the tube dimensions described above and using water as the wash fluid, wash fluid pressure in the range of 5-10 psi, which induces wash fluid velocity of about 3-6 m/sec from each port at a flowrate of about 0.07-0.15 cc/sec from each port, has been found to be effective.

10 A moderate vacuum is preferably applied to the bottom of the tube during pin washing, producing air flow simultaneous with the wash fluid stream introduction as shown in FIGURE 10. The vacuum directs the wash fluid down and out of the tube toward the vacuum plenum chamber 126 of the assembly 102 rather than up toward the printhead. Pins are typically slidably mounted in printheads.

15 The mechanical tolerances of the pins sliding in the printhead are such that even a little wash fluid on the shaft of the pin where it slides in the printhead will cause the pin to stick. Therefore, sufficient vacuum to inhibit wash fluid from flowing or splashing out of the top of the tube toward the printhead is advantageous. Also, the airflow during washing imparts tangential velocity to the wash fluid on the pin surface increasing the effectiveness of washing. However, a limited vacuum is

20 applied as high air velocity (over about 10 m/sec.) can cause the wash streams to deviate away from the pin and into the direction of air flow. If the air velocity is too high and wash fluid velocity too low, the wash fluid can flow down the inside of the tube without contacting the pin. During the washing step, vacuum sufficient to

25 produce air velocity in the range of 0.1 to about 5 m/sec in the tubes is sufficient to entrain the wash fluid without excessively deviating the streams away from the pin.

If a user desires to apply a high vacuum (e.g., a full drying vacuum as used in

the subsequent drying process) during pin washing to further increase washing turbulence, the wash fluid pressure is increased so that the wash fluid stream velocity is sufficient to allow the stream to traverse the cross-flowing air stream and strike the pin. Insufficient wash fluid pressure in this case can cause the wash fluid to stay in contact with the tube's inner wall, and simply run down the inside diameter of the tube without sufficiently contacting the pin. Wash fluid pressure above about 20 psi with the tube dimensions described above is sufficient to drive the wash streams against the pin even with a full drying vacuum activated.

In ordinary operation of the washer/dryer assembly 102, wash fluid is delivered to all washer-dryer tubes 120 in the assembly simultaneously, regardless of whether or not a pin has been installed in the printhead position corresponding to each tube. Printheads are often not fully populated with pins for various reasons. (For instance, a user might not wish to create a microarray with a large footprint, thereby easing the control of hybridization downstream.) In order to avoid wastage of wash fluid, the system is optionally configured to supply wash fluid to only select tubes or groups of tubes in the assembly. For this purpose, the assembly housing is optionally equipped with internal barriers to separate tubes or group of tubes into zones such that fluid is supplied only to particular zones in the assembly as desired. As illustrated in FIGURE 7, the assembly is optionally provided with multiple wash fluid input ports, each leading to a respective zone. One or more washer zone select valves 150 are provided to control wash fluid flow to each zone.

After the washing process, the pressure on the wash fluid is removed, causing the flow of the streams through the wash fluid ports in the tubes to stop. The vacuum for drying the pins is then applied by the vacuum pump 110, causing air to flow through the annular gap between the pins and the tube walls. Vacuum sufficient to produce air velocities of about 50 m/sec or more effectively dries pins in a few seconds. The following table shows examples of two apparatus designs that

dry water from "Telechem Chipmaker 2" pins in two seconds or less, with ambient humidity about 40% RH:

	Washer Tube I.D. 2.3 mm	Washer Tube I.D. 3.0 mm
Number of washer tubes in wash/dry assembly	48	48
Area of each tube I.D.	4.2 mm ² (0.006 in ²)	7.1 mm ² (0.011 in ²)
Total area of all tubes	202 mm ² (0.31 in ²)	340 mm ² (0.53 in ²)
Pump Model	Gast Regenair R1102	Gast Regenair R4110-2
Volume flow rate of air	46 m ³ /hr (27 cfm)	156 m ³ /hr (92 cfm)
Average velocity of air in tubes	64 m/sec	128 m/sec

5 Many types of vacuum pumps are available including, e.g., rotary vane, linear piston, diaphragm, and other types. Regenerative blower type pumps are particularly suitable for generating the flow rates and velocities above. The vacuum pumps used in the above tests were the Gast Regenair Models R1102 (27 cfm) and R4110-2 (92 cfm), from both the Gast Manufacturing Corporation, Benton Harbor MI
10 49023.

To move air at these flow rates, the valves, fittings, tubes, etc. that are between the vacuum pump 110 and the washer/dryer assembly 102 are configured not to excessively restrict the air flow. One guideline to avoid excessive air flow restriction is to design the cross-sectional area of the tubes, fittings, etc. to be at least
15 as large as the total area of all of the tubes 120 in the washer/dryer. In the case of the 2.3 mm tubes and a 48-pin assembly used in the table above, that total area is about 202 mm² (0.31 in²). (A single circular cross section with that area is about 16 mm or 0.63 inches in diameter.) The configuration with the 3 mm diameter tubes and 92 cfm vacuum pump in the table above operates with only 1.5" mercury air
20 pressure drop across the washer/dryer assembly using these guidelines.

The wash fluid with the residue washed from the pins is removed from the washer/dryer assembly 102 by the vacuum system. This liquid is separated from the air before it reaches the vacuum pump 110. This is accomplished by directing the mixed air/wash fluid stream to the container 106 where the air velocity slows sufficiently to allow the liquid to settle to the bottom. A 5.25-gallon polymer lab carboy (available from Cole Parmer P-06063-22, Cole Parmer Instrument Co., Vernon Hills IL 60061) with fill-vent caps is an example of a suitable container 106. The incoming mixed air/wash fluid stream is directed through a cap of the container 106 downward towards the bottom. An air outlet to the vacuum pump is at the top of the container (also in the cap) and draws in air with very little wash fluid mixed in.

Various modifications to the wash-dry cycle described above are possible. For example, instead of applying the multiple-jet wash once followed by a thorough drying, a plurality of quick pulse-type wash actions can be applied to the pin with some drying between wash pulses. For pins that can only take wash fluid into the slot via capillary action, this multi-pulse wash cycle could be advantageous in serially diluting the residue in the slot.

It also may be advantageous to utilize the printhead's motion control system to impart small motions to the pins during the wash/dry process. Moving the pins vertically (along the pin axes) a few millimeters or transversely a fraction of a millimeter or so can further increase the turbulence of the wash fluid flow on the pin surface. A small vertical move between the wash and dry operations may also enhance pin drying by placing the pin tip in a location in the tube that has higher air turbulence. Small motions such as these take only a fraction of a second and do not significantly add to the wash/dry cycle time.

The inventive washer/dryer system can be used with multiple types of wash fluids as desired. For example, pins could be washed with a detergent solution followed by a water rinse. Also, instead of a steady stream of wash fluid directed

to pins, wash fluid can be delivered in pulses by rapidly opening and closing a valve at the wash fluid input to the washer/dryer assembly 102. Alternatively, an aerosol of wash fluid could be used by injecting pressurized air or other gas into the wash fluid.

5 As previously mentioned, the environment inside the microarray spotter enclosure generally has controlled humidity in the 55% - 65% range. The vacuum drying process in accordance with the invention is preferably made quicker and more effective by allowing the pin washer-dryer 100 to be primarily supplied with lower-humidity air from outside the enclosure as illustrated in the block diagram of
10 FIGURE 14. As previously mentioned, air in typical office and laboratory environments is in the 30%-45% range. By placing the washer-dryer apparatus 100 near an outside wall of the enclosure 21, it is relatively easy to configure a vent and ducting 160 in the enclosure 21 that allows outside air to be drawn in by the dryer of the apparatus 100. It is advantageous to place a filter 162 in this venting
15 arrangement to reduce the entry of dust into the drying air stream. Air from the dryer is exhausted outside the enclosure through a ducting 164.

While air is described as the gas used for drying pins, it should be noted that use of other sourced gases is also possible. Such drying gases can include, e.g., dry nitrogen, heated air, or otherwise dried air.

20 Since certain changes may be made in the above apparatus without departing from the scope of the invention herein involved, it is intended that all matter contained in the above description or shown in the accompanying drawing shall be interpreted in an illustrative and not a limiting sense.

Claims

1. A method of washing and drying a pin of a microarray spotting instrument, comprising:
moving said pin to a given position;
washing said pin while in said given position; and
drying said pin without substantially moving said pin from said given position.
2. The method of Claim 1 wherein moving the pin comprises positioning said pin in a given location in a pin washer/dryer apparatus.
3. The method of Claim 2 wherein said given location comprises a chamber for receiving the pin.
4. The method of Claim 3 wherein said chamber is defined by a tube.
5. The method of Claim 1 wherein washing the pin comprises directing at least one stream of wash fluid at the pin.
6. The method of Claim 5 wherein said stream velocity is approximately 3 m/sec.
7. The method of Claim 5 wherein multiple streams of wash fluid are directed at a tip of said pin.
8. The method of Claim 7 wherein the streams are directed in a swirling pattern.
9. The method of Claim 1 wherein said position comprises a tube interior, and

wherein washing the pin comprises directing a stream of wash fluid at the pin through an aperture in the tube.

10. The method of Claim 9 further comprising applying a vacuum to the tube to draw wash fluid out of the tube and away from a printhead holding the pin while directing the stream of wash fluid at the pin.

11. The method of Claim 1 wherein drying said pin comprises flowing air past said pin.

12. The method of Claim 11 wherein the air is flowed at a speed greater than 20 m/sec.

13. The method of Claim 11 wherein said position comprises a tube interior, and wherein flowing air comprises applying a vacuum to the tube to draw air through the tube.

14. The method of Claim 1 wherein said pin includes a pin tip having a slot reservoir for holding sample material to be deposited on a microarray substrate, and wherein washing the pin comprises directing a stream of wash fluid at the slot reservoir.

15. The method of Claim 1 wherein washing the pin comprises impacting said pin with pulsed streams of wash fluid.

16. The method of Claim 15 wherein washing further comprises at least partially drying said pin between applications of said pulsed streams of wash fluid.

17. The method of Claim 1 wherein drying said pin comprises forcing a gas past said pin.
18. The method of Claim 17 wherein said gas comprises air, said air being of lower humidity than air in an enclosure containing the spotting instrument.
19. An apparatus for washing and drying pins in a microarray spotting instrument, comprising a housing having a structure therein defining a plurality of chambers, each for receiving one of the pins of said spotting instrument, said structure including openings leading to said chambers for flowing wash fluid through the chambers for washing pins therein and flowing a gas through the chambers for drying said pins.
20. The apparatus of Claim 19 wherein said structure comprises a plurality of upstanding tubes arranged in said housing.
21. The apparatus of Claim 20 wherein said openings include at least one wash fluid inlet port in each tube for introducing streams of wash fluid into said chamber.
22. The apparatus of Claim 21 wherein each tube includes multiple wash fluid ports around said tube.
23. The apparatus of Claim 22 wherein said multiple wash fluid ports are oriented to direct wash fluid towards the center of said tube.
24. The apparatus of Claim 22 wherein said multiple wash fluid ports are oriented to direct wash fluid in a direction offset from the center of said tube to generate a

swirling wash flow pattern.

25. The apparatus of Claim 22 wherein said multiple wash fluid ports are oriented to direct wash fluid in an upward direction inside said chamber.

26. The apparatus of Claim 22 wherein said multiple wash fluid ports are oriented to direct wash fluid in a downward direction inside said chamber.

27. The apparatus of Claim 19 further comprising means for supplying wash fluid to said housing.

28. The apparatus of Claim 27 wherein said means for supplying wash fluid comprises an air compressor for providing pressurized wash fluid from a wash fluid container.

29. The apparatus of Claim 27 wherein said means for supplying wash fluid comprises a pump for providing pressurized wash fluid from a wash fluid container.

30. The apparatus of Claim 29 wherein said pump comprises a gear pump.

31. The apparatus of Claim 19 wherein said structure partitions groups of said chambers such that wash fluid can be selectively applied to particular groups of chambers.

32. The apparatus of Claim 31 further comprising at least one selector valve for selectively directing wash fluid to one or more particular groups of chambers.

33. The apparatus of Claim 19 wherein the gas comprises air.
34. The apparatus of Claim 19 further comprising means for flowing the gas across surfaces of pins in said chamber.
35. The apparatus of Claim 34 wherein said means for flowing the gas comprises a vacuum pump for drawing air through said chambers.
36. The apparatus of Claim 19 further comprising a generally sealed enclosure around said apparatus, said enclosure including an inlet port for receiving at least some of the gas from outside said enclosure to be used for drying said pins.
37. The apparatus of Claim 36 further comprising a filter at said inlet port for filtering the gas.
38. The apparatus of Claim 36 further comprising an outlet port in said enclosure for releasing gas used for drying said pins outside said enclosure.
39. The apparatus of Claim 19 further comprising a receptacle for collecting wash fluid and gas from said chambers.
40. The apparatus of Claim 39 wherein said receptacle comprises a vacuum plenum chamber.
41. The apparatus of Claim 39 further comprising a vacuum pump for drawing wash fluid and gas out of said receptacle.

42. The apparatus of Claim 41 further comprising a waste fluid container between said vacuum pump and said receptacle for separating gas from said wash fluid.

43. The apparatus of Claim 19 wherein said structure comprises a plurality of upstanding tubes arranged in said housing with each chamber comprising a tube interior, for each tube said openings comprise at least one wash fluid inlet port in a tube wall and axial end openings at opposite upper and lower axial ends of the tube, said opening at the upper axial end of the tube for receiving a pin tip and gas flow, and said opening at the lower axial end of the tube for discharging wash fluid and gas from said chamber.

44. The apparatus of Claim 43 wherein multiple wash fluid inlet ports are arranged radially around said tube wall.

45. A method of washing pins in a microarray spotting instrument, comprising:
moving the pins to a given position; and
impacting tips of said pins with streams of wash fluid.

46. The method of Claim 45 further comprising drying said pins without substantial movement of said pins from said given position.

47. The method of Claim 46 wherein drying said pins comprises flowing a gas past said pins.

48. The method of Claim 47 wherein said gas comprises air.

49. The method of Claim 47 wherein the gas is flowed at a speed greater than 20

m/sec.

50. The method of Claim 46 wherein moving the pins comprises positioning said pins in a given locations in a pin washer/dryer apparatus.

51. The method of Claim 50 wherein said given locations comprise a plurality of chambers, each for receiving one of said pins.

52. The method of Claim 51 wherein said chambers are defined by an array of upstanding tubes.

53. The method of Claim 45 wherein the streams are directed in a swirling pattern.

54. The method of Claim 45 further comprising applying a vacuum to draw wash fluid away from the pins as the pins are impacted with the streams of wash fluid.

55. The method of Claim 45 wherein said pin tips each have a slot reservoir for holding sample material to be deposited on a microarray substrate, and wherein the streams of wash fluid are directed at the slot reservoirs.

56. The method of Claim 45 wherein impacting the pin tips comprises impacting the pin tips with pulsed streams of wash fluid.

57. The method of Claim 56 further comprising at least partially drying said pins between applications of said pulsed streams of wash fluid.

58. The method of Claim 45 further comprising drying said pins by forcing air

across surfaces of said pins, said air being of lower humidity than air in an enclosure containing the spotting instrument.

59. A microarray spotting instrument comprising:
- a printhead for holding a plurality of pins;
 - a substrate station for holding at least one microarray substrate;
 - a well station for holding sample material to be deposited on said at least one microarray substrate using said printhead;
 - an apparatus for washing and drying the pins comprising a housing having a structure therein defining a plurality of chambers, each for receiving one of said pins, said structure including openings leading to said chambers for flowing wash fluid through the chambers for washing pins therein and flowing a gas through the chambers for drying said pins; and
 - a positioning mechanism for moving said printhead relative to said substrate station, said well station and said apparatus for washing and drying pins.
60. The microarray spotting instrument of Claim 59 wherein said structure in said apparatus comprises a plurality of upstanding tubes arranged in said housing.
61. The microarray spotting instrument of Claim 60 wherein said openings in said apparatus include at least one wash fluid inlet port in each tube for introducing wash fluid into said chambers.
62. The microarray spotting instrument of Claim 61 wherein each tube includes multiple wash fluid ports around said tube.
63. The microarray spotting instrument of Claim 62 wherein said multiple wash

fluid ports are oriented to direct wash fluid towards the center of said tube.

64. The microarray spotting instrument of Claim 62 wherein said multiple wash fluid ports are oriented to direct wash fluid in a direction offset from the center of said tube to generate a swirling wash flow pattern.

65. The microarray spotting instrument of Claim 62 wherein said multiple wash fluid ports are oriented to direct wash fluid in an upward direction inside said chamber.

66. The microarray spotting instrument of Claim 62 wherein said multiple wash fluid ports are oriented to direct wash fluid in a downward direction inside said chamber.

67. The microarray spotting instrument of Claim 59 wherein said apparatus further comprises means for supplying wash fluid to said housing.

68. The microarray spotting instrument of Claim 67 wherein said means for supplying wash fluid comprises an air compressor for providing pressurized wash fluid from a wash fluid container.

69. The microarray spotting instrument of Claim 67 wherein said means for supplying wash fluid comprises a pump for providing pressurized wash fluid from a wash fluid container.

70. The microarray spotting instrument of Claim 69 wherein said pump comprises a peristaltic pump.

71. The microarray spotting instrument of Claim 59 wherein said structure in said apparatus partitions groups of said chambers such that wash fluid can be selectively applied to particular groups of chambers.

72. The microarray spotting instrument of Claim 71 wherein the apparatus further comprises at least one selector valve for selectively directing wash fluid to one or more particular groups of chambers.

73. The microarray spotting instrument of Claim 59 wherein the apparatus further comprises means for flowing gas across surfaces of pins in said chambers.

74. The microarray spotting instrument of Claim 73 wherein said means for flowing gas comprises a vacuum pump for drawing gas through said chambers.

75. The microarray spotting instrument of Claim 59 further comprising a generally sealed enclosure around said instrument, said enclosure including an inlet port for introducing gas outside said enclosure into said apparatus for drying said pins.

76. The microarray spotting instrument of Claim 75 further comprising a filter at said inlet port for filtering the gas.

77. The microarray spotting instrument of Claim 76 further comprising an outlet port in said enclosure for releasing gas used for drying said pins outside said enclosure.

78. The microarray spotting instrument of Claim 59 wherein said apparatus further

comprises a receptacle for collecting wash fluid and gas from said chambers.

79. The microarray spotting instrument of Claim 78 wherein said receptacle comprises a vacuum plenum chamber.

80. The microarray spotting instrument of Claim 78 further comprising a vacuum pump for drawing wash fluid and gas out of said receptacle.

81. The microarray spotting instrument of Claim 80 further comprising a waste fluid container between said vacuum pump and said receptacle for separating gas from said wash fluid.

82. The microarray spotting instrument of Claim 59 wherein said structure of said apparatus comprises a plurality of upstanding tubes arranged in said housing with each chamber comprising a tube interior, for each tube said openings comprise at least one wash fluid inlet port in a tube wall and axial end openings at opposite upper and lower axial ends of the tube, said opening at the upper axial end of the tube for receiving a pin tip and gas flow, and said opening at the lower axial end of the tube for discharging wash fluid and gas from said chamber.

83. The microarray spotting instrument of Claim 82 wherein multiple wash fluid inlet ports are arranged radially around said tube wall.

84. A method of using a microarray spotting instrument, comprising:

- (a) dipping tips of pins mounted in the printhead into a reservoir of target material;
- (b) positioning the printhead over a microarray substrate to be spotted;

- (c) lowering the printhead to bring the tips of the pins into contact with the substrate to print spots on the substrate;
- (d) raising the printhead to separate the pins from the substrate;
- (e) moving the printhead to position at least a portion of the pins in a washer/dryer apparatus;
- (f) washing the pins; and
- (g) drying the pins without substantial movement of said pins relative to the washer/dryer apparatus.

85. A method of using a microarray spotting instrument, comprising:

- (a) dipping tips of pins mounted in the pinhead into a reservoir of target material;
- (b) positioning the printhead over a microarray substrate to be spotted;
- (c) lowering the printhead to bring the tips of the pins into contact with the substrate to print spots on the substrate;
- (d) raising the printhead to separate the pins from the substrate;
- (e) moving the printhead to position at least a portion of the pins in a washer/dryer apparatus;
- (f) washing said pins by impacting tips of said pins with streams of wash fluid; and
- (g) drying said pins.

86. A method of using a microarray spotting instrument, comprising:

- (a) dipping tips of pins mounted in the pinhead into a reservoir of target material;
- (b) positioning the printhead over a microarray substrate to be spotted;
- (c) lowering the printhead to bring the tips of the pins into contact with the

substrate to print spots on the substrate;

(d) raising the printhead to separate the pins from the substrate;

(e) moving the printhead to position at least a portion of the pins in a washer/dryer apparatus;

(f) washing said pins; and

(g) drying said pins with gas introduced from outside an enclosure containing said microarray spotting instrument.

87. The method of Claim 86 wherein said gas comprises air.

88. The method of Claim 86 wherein said gas comprises nitrogen.

89. The method of claim 86 wherein (g) comprises flowing the gas over pin surfaces at gas velocities greater than 20 m/sec.

90. A microarray spotting instrument comprising:

a printhead for holding a plurality of pins;

a substrate station for holding at least one microarray substrate;

a well station for holding sample material to be deposited on said at least one microarray substrate using said printhead;

an apparatus for washing and drying the pins;

a positioning mechanism for moving said printhead relative to said substrate station, said well station and said apparatus for washing and drying pins; and

an enclosure containing said printhead, substrate station, well station, apparatus for washing and drying, and positioning mechanism, said enclosure including an inlet port connected to said apparatus for introducing gas from outside said enclosure for use in drying said pins, said enclosure also including an outlet port connected to said

apparatus for discharging the gas.

91. The microarray spotting instrument of Claim 90 wherein said gas comprises air.

92. The microarray spotting instrument of Claim 90 wherein said gas comprises nitrogen.

93. The microarray spotting instrument of Claim 90 wherein said apparatus flows the gas over pin surfaces for drying said pins at gas velocities greater than 20 m/sec.

94. An apparatus for washing and drying pins in a microarray spotting instrument, comprising:

a housing having a structure therein defining a plurality of chambers, each for receiving one of the pins of said spotting instrument, said structure including openings leading to said chambers for flowing wash fluid and gas through the chambers for washing and drying pins therein; and

a device for applying a vacuum to said chambers for evacuating the wash fluid and gas from said chambers.

95. The apparatus of Claim 94 wherein said device comprises a vacuum pump.

96. A method of washing pins in a microarray spotting instrument, comprising:
moving the pins to a given position;

impacting said pins with streams of wash fluid; and

flowing gas past said pins while impacting said pins with wash fluid to increase turbulence to assist in removal of residual sample from said pins.

97. The method of Claim 96 wherein said gas imparts tangential velocity to the wash fluid on pin surfaces to increase effectiveness of said washing.

98. The method of Claim 96 further comprising slightly reciprocating said pins while being washed.

99. The method of Claim 1 further comprising slightly reciprocating said pin while being washed.

100. The method of Claim 1 further comprising slightly reciprocating said pin while being dried.

101. The method of Claim 45 further comprising slightly reciprocating said pins while being impacted with wash fluid.

METHOD AND APPARATUS FOR WASHING AND DRYING PINS IN MICROARRAY SPOTTING INSTRUMENTS

Abstract of the Disclosure

A method and apparatus are provided for washing and drying pins in a microarray spotting instrument. The apparatus includes an array of chambers, each for receiving one of the pins of the spotting instrument. To wash the pins, streams of wash fluid are directed at the pins. To dry the pins, a gas such as air is flowed over pin surfaces.

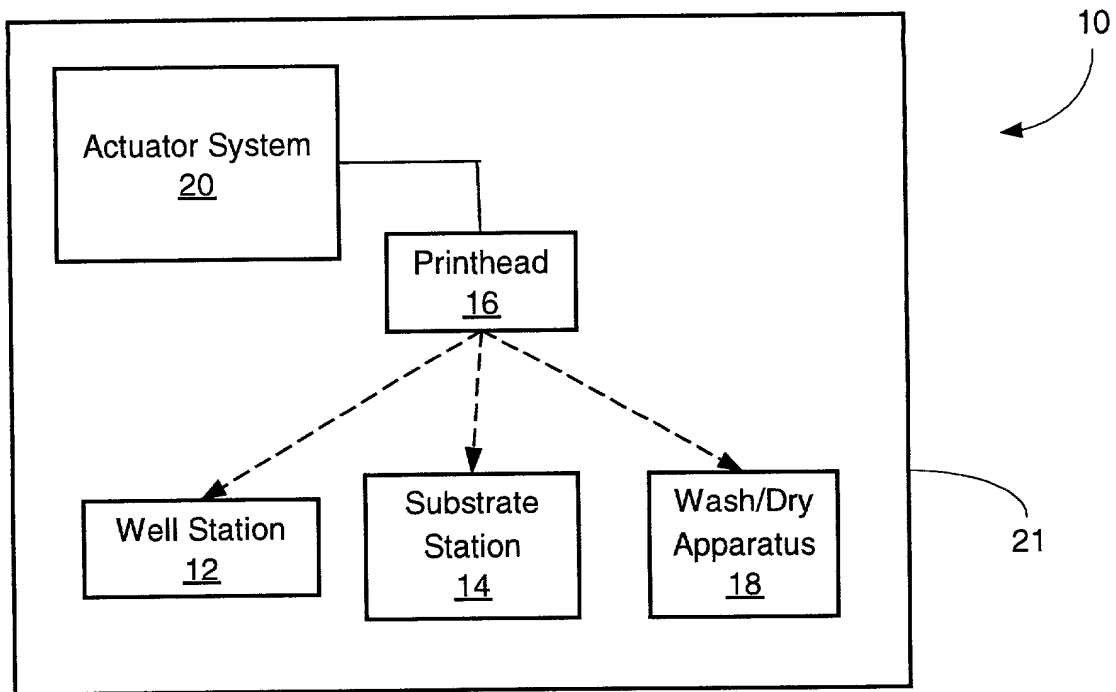


Fig. 1
Prior Art

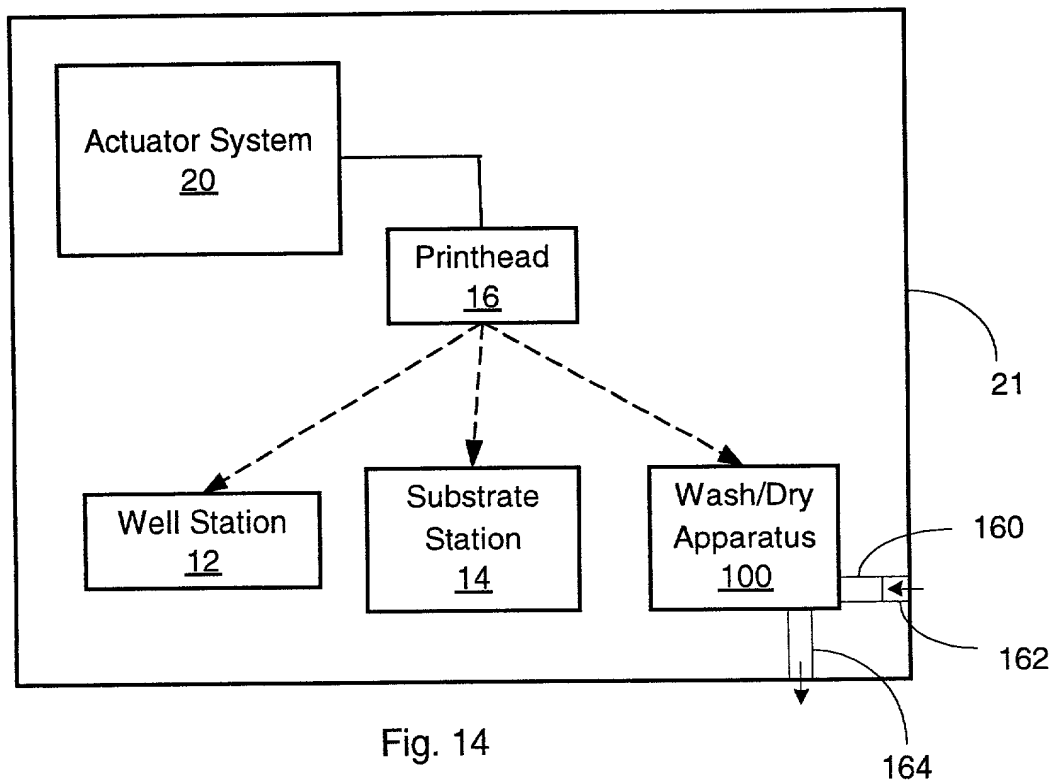


Fig. 14

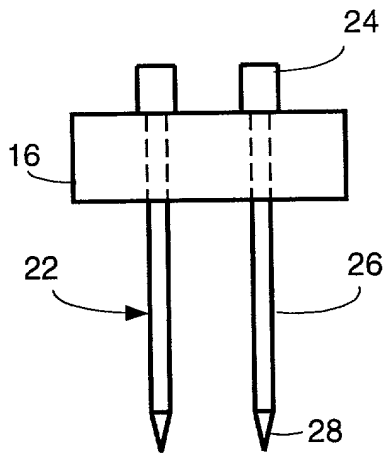


Fig. 2
Prior Art

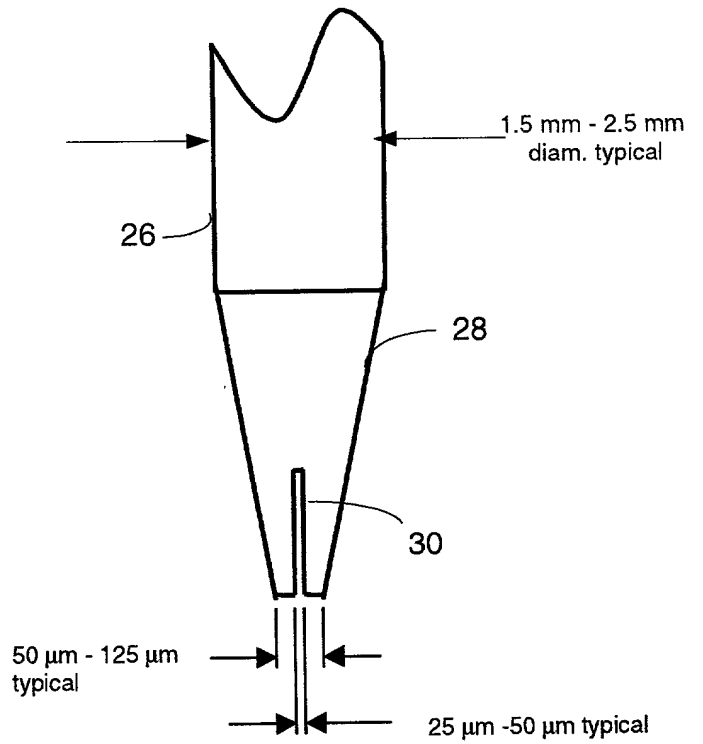


Fig. 3
Prior Art

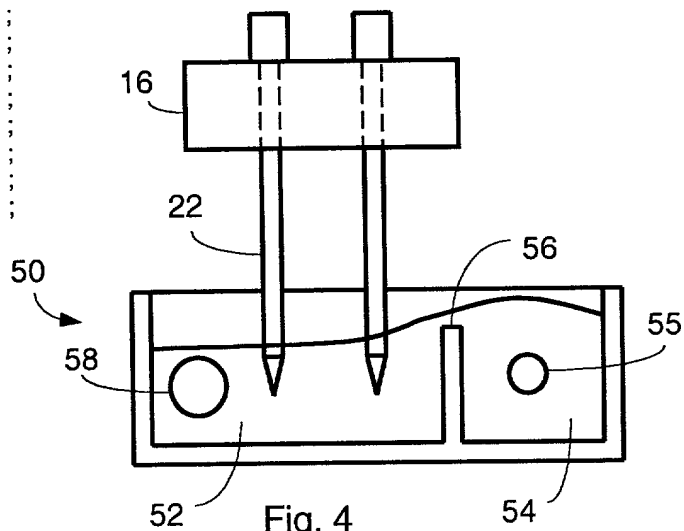


Fig. 4
Prior Art

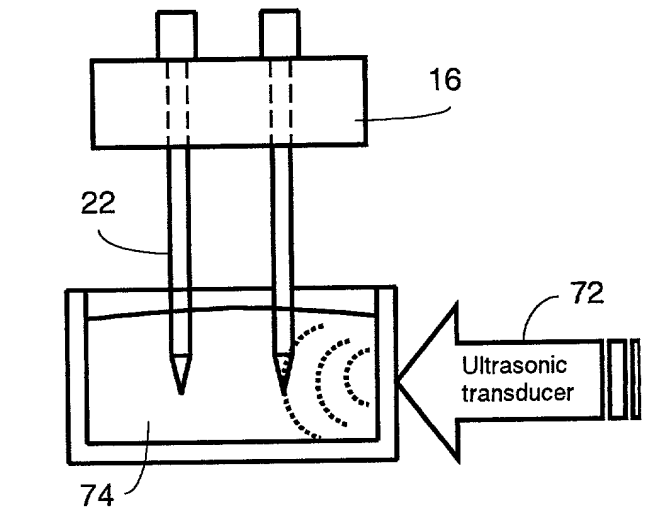


Fig. 5
Prior Art

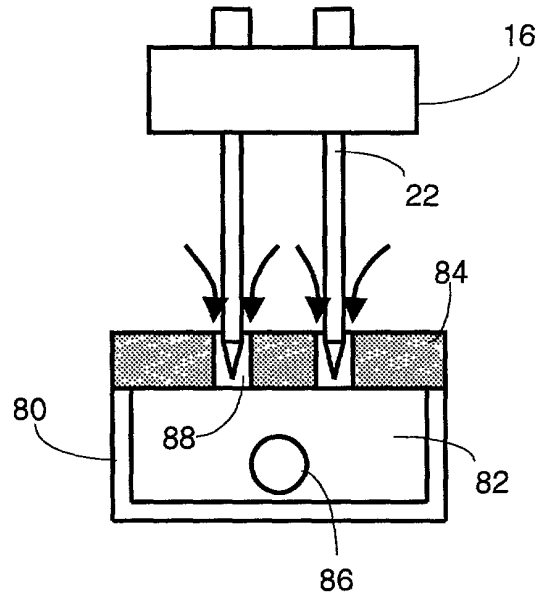


Fig. 6
Prior Art

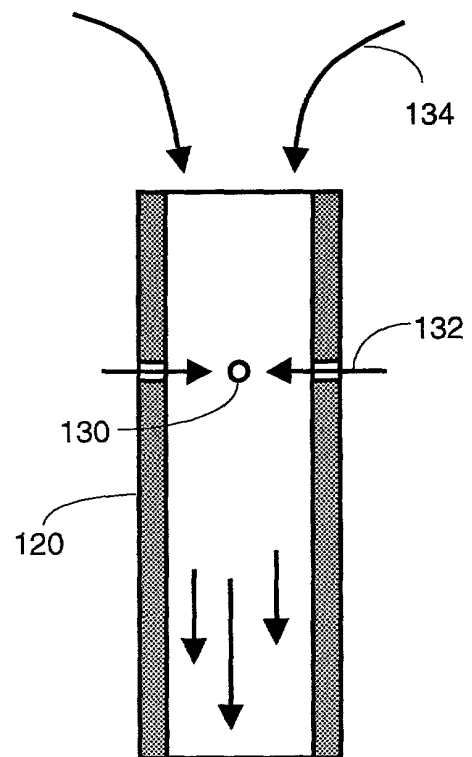
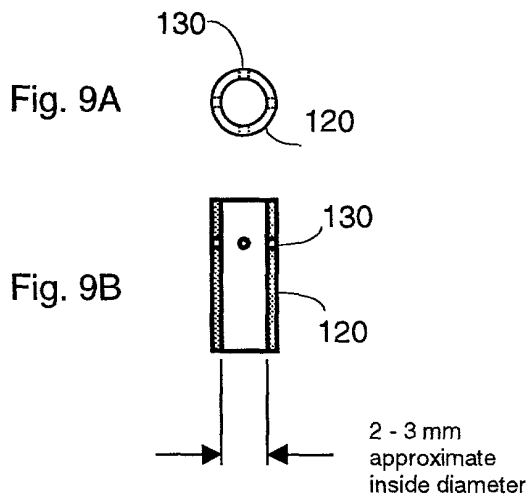


Fig. 10

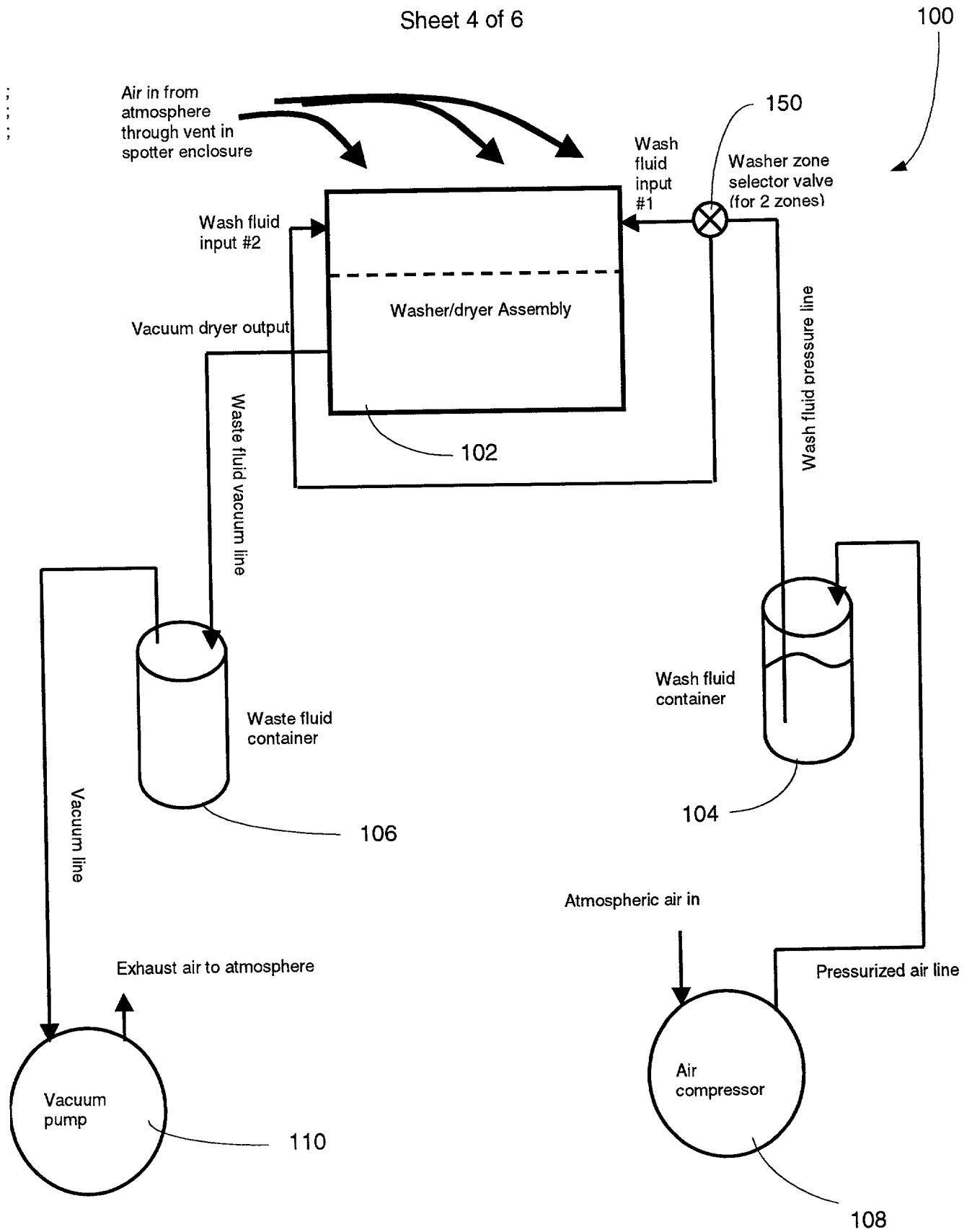
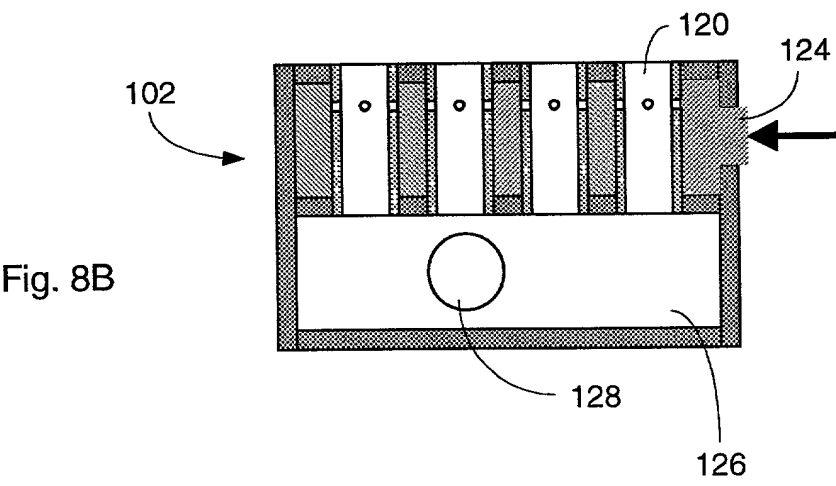
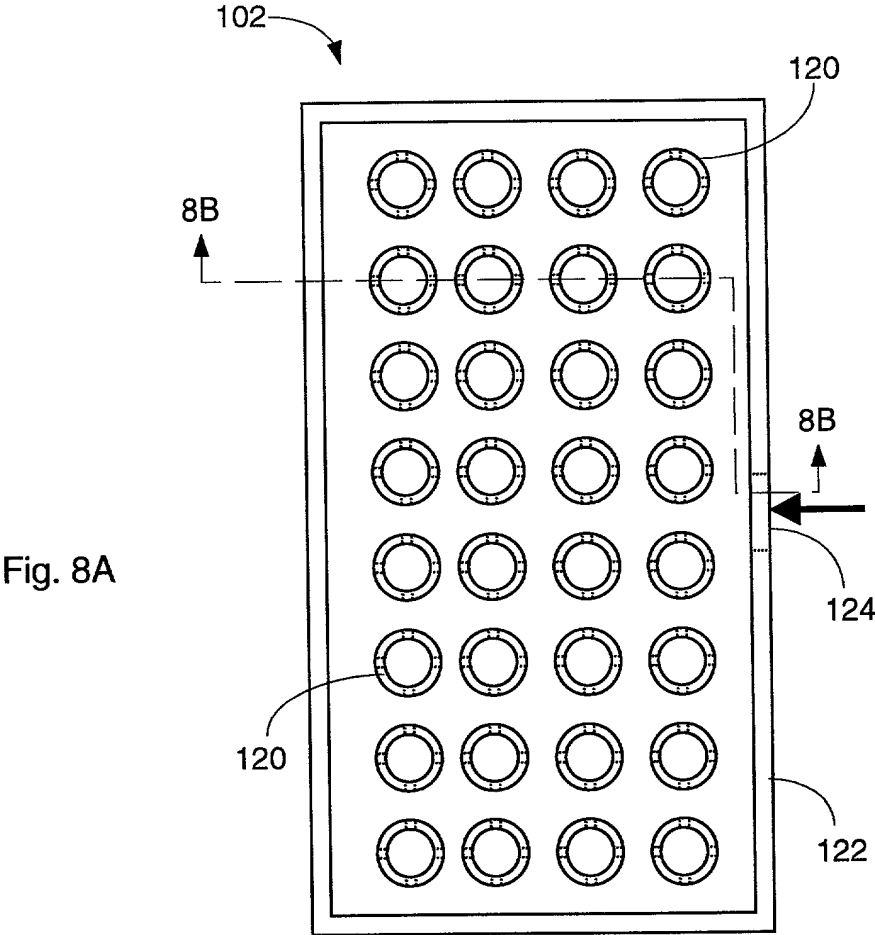


Fig. 7



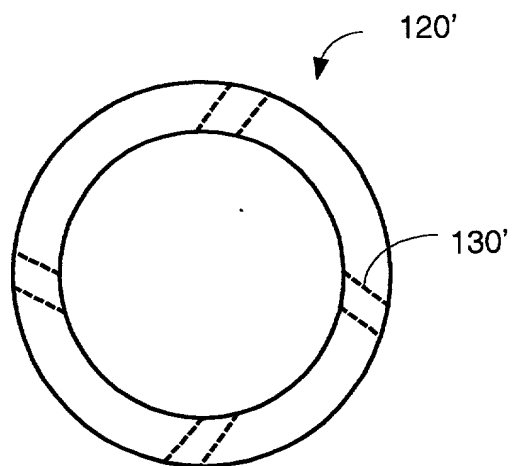


Fig. 11

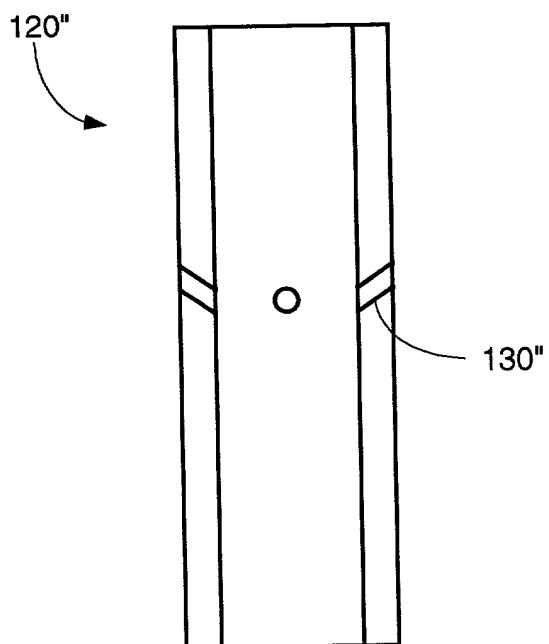


Fig. 12

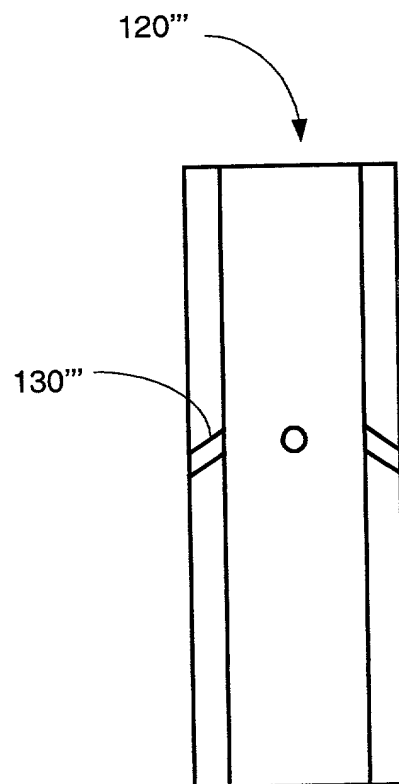


Fig. 13

DECLARATION AND POWER OF ATTORNEY

As below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled:

METHOD AND APPARATUS FOR WASHING AND DRYING PINS IN MICROARRAY SPOTTING INSTRUMENTS

the specification of which (check only one):

☒ is attached hereto.

☐ was filed as United States Patent Application
Serial No. _____
on _____
and was amended
on _____
(if applicable)

☐ was filed as PCT Patent Application
Serial No. _____
on _____
and was amended under PCT Article 19
on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s)

designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS
UNDER 35 U.S.C. §119(a)-(d) or 365(b), or 365(a):

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 U.S.C. §119 (YES/NO)

I hereby claim benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)	
		<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or 365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information that is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior applications and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATION OR PCT INTERNATIONAL APPLICATION(S)
DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120 or 365(c):

APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS: (PATENTED, PENDING OR ABANDONED)

POWER OF ATTORNEY: As named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James B. Lampert	Reg. No. 24,564
Wayne M. Kennard	Reg. No. 30,271
Michael J. Bevilacqua	Reg. No. 31,091
Holly L. Baker	Reg. No. 31,321
Henry N. Wixon	Reg. No. 32,073

Donald R. Steinberg	Reg No. 37,241
Wayne A. Keown, Ph.D.	Reg. No. 33,923
Ann-Louise Kerner, Ph.D.	Reg. No. 33,523
Michael A. Diener	Reg. No. 31,122
Colleen Superko	Reg. No. 39,850
Richard Goldenberg	Reg. No. 38,895
Gretchen Rice, Ph.D.	Reg. No. 37,429
Peter M. Dichiara	Reg No. 38,005
Scott M. Alter	Reg. No. 39,850
Barbara A. Barakat	Reg. No. 32,190
Edward D. Grieff	Reg. No. 38,898
Jason A. Reyes	Reg. No. 41,513
Rajesh Vallabh	Reg. No. 35,761
Nancy Chiu, Ph.D.	Reg. No. 43,545
Keum J. Park	Reg. No. 42,059
Janice M. Klunder, Ph.D.	Reg. No. 41,121
Ayla A. Lari	Reg. No. 43,739

the mailing address and telephone number of each of whom is HALE AND DORR, 60 State Street, Boston, Massachusetts 02109, (617) 526-6000.

Send Correspondence to:

Rajesh Vallabh

HALE AND DORR LLP

60 State Street

Boston, Massachusetts 02109

Direct Telephone Calls to:

Rajesh Vallabh

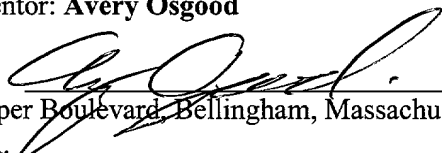
(617) 526-6000 (Telephone)

(617) 526-5000 (Facsimile)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: **Avery Osgood**

Inventor's signature



Date 6/3/01

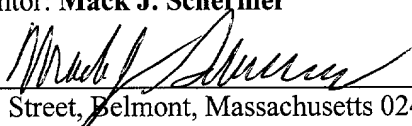
Residence: 8 Harper Boulevard, Bellingham, Massachusetts 02019

Citizenship: U.S.A.

Post Office Address: 8 Harper Boulevard, Bellingham, Massachusetts 02019

Full name of second inventor: **Mack J. Schermer**

Inventor's signature



Date June 2, 2000

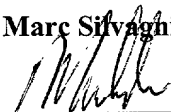
Residence: 284 Lake Street, Belmont, Massachusetts 02478

Citizenship: U.S.A.

Post Office Address: 284 Lake Street, Belmont, Massachusetts 02478

Full name of third inventor: **Marc Silvagni**

Inventor's signature



Date 6/2/00

Residence: 2 Marshall Road, Beverly, Massachusetts 01915

Citizenship: U.S.A.

Post Office Address: 2 Marshall Road, Beverly, Massachusetts 01915

rajesh vallabh - z:\legal\docs~f\109629.116\joint inventor declaration.doc